02911.000600. PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

OLUWOLE T. ALOBA ET AL.

Application No.: 10/023,748

Filed: December 21, 2001

For: ORAL PHARMACEUTICAL PRODUCTS CONTAINING 17β-ESTRADIOL-3-LOWER ALKANOATE, METHOD OF ADMINISTERING THE SAME AND PROCESS OF PREPARATION

Examiner: San Ming R. Hui

Group Art Unit 1617

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SECOND DECLARATION UNDER 37 C.F.R. §1.132

Sir:

Tina M. deVries, declares and says that:

1. I am the Vice President of Pharmaceutics at Galen Holdings, PLC and have been in this position since November 2000. Prior to this, I was the Senior Director of Research and Development of Pharmaceutics at Warner-Chilcott, which was eventually acquired by Galen Holdings.

2. I graduated from The Ohio State University Graduate School in 1989, with a Doctor of Philosophy in Pharmaceutics and Pharmaceutical Chemistry.

3. I am one of the named inventors of the above-identified United States Patent Application.

4. I am aware that the Examiner has rejected claims 1, 5 and 10-11 under 35 U.S.C. 103(a) as being allegedly unpatentable over U.S. Patent No. 3,478,070 (Stein et al.) and claims 4, 6-9 and 46-47 over Stein in view of Remington, March and Wolfe. I am also aware of the Examiner's assertion that it would have been obvious to add acetic acid to the solid dosage form of the present invention. I respectfully disagree with the Examiner's position and under my supervision and direction have had tests conducted to show the unexpected advantages achieved when using acetic acid in a solid dosage form of 17-ß-estradiol-3-acetate.

5. Tablets containing 0.45 mg 17-ß-estradiol-3-acetate were formulated with and without acetic acid. The acetic acid containing tablets contained 0.002 mg of glacial acetic acid, but otherwise were substantially identical in content. Tablet samples from each formulation were bottle packaged (100 tablets per bottle) in 60cc HDPE bottles containing 2g of silica dessicant. Bulk and bottle packaged tablet samples were stored under temperature and humidity conditions likely to induce hydrolytic degradation. The bulk tablets were stored in open glass beakers at 50°C/75% RH, and the bottled tablets were stored at 40°C/≥75% RH. The tablets were tested periodically for levels of estradiol (the primary hydrolysis product) and other degradation products.

6. The test data obtained for the tablets in the open beakers are set forth in Table 1.

TABLE 1

	Estradiol Acetate (% label claim)		Estradiol (% label claim)		Total Related Substances (% label claim)	
Formulation	AA	w/out AA	AA	w/out AA	AA	W/out AA
Expected 0 Day Value	105.0	105.0	0	0	0	0
0 days	104.4	94.2	0.32	4.4	0.7	11.5
3 days	107.2	90.1	1.0	3.6	1.9	13.6
7 days	99.5	87.1	2.8	6.2	3.5	17.3
14 days	98.2	82.7	6.2	7.8	7.3	21.5
21 days	93.1	79.1	9.9	9.9	11.1	25.3
28 days	87.4	76.8	14.1	12.1	15.7	30.2

AA is acetic acid

Surprisingly, the results show that the acetic acid (AA) containing formulation showed a particularly improved stability for 17-ß-estradiol-3-acetate after the manufacturing of the tablets. Moreover, while the amount of measured estradiol in the acetic acid formulation surpassed the concentration of estradiol in the acetic acid free formulation after 28 days, it can be seen by reference to the estradiol acetate content and total related substances content, i.e., degradation products, that the acetic acid formulation was superior in initial and ongoing stability compared to the acetic acid free formulation.

7. The test data obtained for the tablets stored in the bottles are set forth in Table 2.

TABLE 2

	Estradiol Acetate (% label claim)		Estradiol (% label claim)		Total Related Substances (% label claim)	
Formulation	AA	w/out AA	AA	w/out AA	AA	w/out AA
0 month	104.6	94.2	0.42	4.4	0.75	11.5
1 month	104.5	90.6	0.79	5.4	1.68	14.3

These data also show a large stability improvement for the acetic acid containing solid dosage formulations of 17-ß-estradiol-3-acetate compared to the non-acetic acid formulation. Again, the improved stability is seen both immediately after manufacture of the formulation and during storage.

8. In my opinion, this improved stability found at both the manufacturing step and during storage is an unexpected and significant advantage of the solid dosage form containing acetic acid in combination with 17-ß-estradiol-3-acetate of the present invention. It is particularly unexpected that the inclusion of acetic acid in the solid dosage form of 17-ß-estradiol-3-acetate had such a significant stabilizing effect during the manufacture of the dosage form. Based on these results, it is also my opinion, that a similar improvement in stability will be found using the other acid hydrolysis inhibitors described in the present specification.

9. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Subscribed this 26 day of May, 2004.

Tina deVries, Ph.D

NY_MAIN430159_1.DOC